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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/127,364	YEDNOCK ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of the amendment filed 9/22/03, claims 24-30 have been cancelled, claims 31, 32, 34, 36 amended, and claims 37-47 added. Claims 31-47 are pending. Applicants' arguments filed 9/22/03 have been considered and found not persuasive.

Applicants are reminded that a listing of all claims is required, not just some of them.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 39 recites that there are alpha-9 antagonists which bind osteopontin, tenascin, or VCAM-1. However, it does not appear to be descriptive support for this. The passages on page 3, lines 8-11 and page 4, lines 8-12 are noted, but these pertain to the binding between alpha 9 and the cited proteins, not to binding between an alpha-9 antagonist and the cited proteins. Applicants are requested to point out the page and line number where support may be found.

*

Claims 31-40, 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As stated on page 32, line 3+, each of the compounds of examples 1-373 of application 08/904424 exhibited an IC_{50} of 15 micromolar or less in an assay which measures antagonism of the compounds to VLA-4. It does not appear that applicants have tested the compounds in an assay of alpha-9 integrin antagonism; if applicants are asserting that there exists a correlation between the propensity of a compound to antagonize VLA-4, and the propensity of the compound to antagonize *alpha*-9 integrin, such an assertion will be left unchallenged at the present time. However, to the extent that such overlap exists, a finding of unpredictability in VLA-4 antagonism will extend to alpha-9 antagonism as well.

The assertion by the examiner is that (a) structure/activity relationships in VLA-4 antagonism are unpredictable, and (b) treatment of inflammatory conditions is unpredictable as well. Consider the following:

- Dutta (*Journal of Peptide Science* **6**, 321-341, 2000) has examined the efficacy of various peptides in the antagonism of VLA-4/VCAM-1 binding. As stated on page 329, col 2, last two lines, the following two compounds were inactive both *in vitro* and *in vivo*:

  cyclo[Ile-Leu-Asp-Val-NH $(CH2)_2CO$]
  Ac-cyclo(Orn-Leu-Asp-Val)

  These peptides are minor variations of peptides that were active.

- Arrhenius (*USP 5,688,913*) discloses (cols 17-18) several examples of compounds

which failed to antagonize VLA-4. These compounds are minor variations of other compounds that were potent antagonists of VLA-4.

- Komoriya, Akira (*J. Biol. Chem.* **266** (23), 15075-15079, 1991) discloses that in an assay of $\alpha_4\beta_1$ activity, the pentapeptide EILEV was active, but pentapeptide EILDV was not. This latter peptide differs from the former by just one methylene unit.

- Haworth, Duncan (*Br. J. Pharmacol.* **126**(8), 1751-1760, 1999) discloses various VLA-4 antagonists. At least one of the disclosed compounds was inactive; this compound differed by only a few methylene units from a compound that was active.

- Haubner (*J. Am. Chem. Soc.* **118**, 7881, 1996) discloses (table 2) two compounds which failed to inhibit fibrinogen binding to the $\alpha_{IIb}\beta_1$ receptor, and vitronectin binding to the the $\alpha_V\beta_3$ receptor. The reference also discloses (p. 7882, col 2) that replacement of glycine with alanine in RGD results in a "drastic loss" of activity. These data argue for "unpredictability" in structure activity relationships of integrins generally. In addition, the "unpredictability" in structure activity relationships of RGD-peptides has direct relevance to the claimed compounds. As disclosed in Yang Y (*European Journal of Immunology* **28** (3) 995-1004, 1998) RGD-containing peptides can bind to VLA-4. Thus, if one cannot predict structure activity relationships of RGD peptides in their binding to VLA-4, it stands to reason that such unpredictability extends to other compounds which either do bind VLA-4, or which are asserted to exhibit such an effect.

In addition to the foregoing, the following references teach "failure" in the treatment of one or more inflammatory conditions:

Vatistas N J, "Infection of the intertubercular bursa in horses: four cases (1978-1991)", [*Journal of the American Veterinary Medical Association* **208** (9) 1434-7, 1996];

Tait A, "Synthesis and antiinflammatory activity of 2,6-bis(1,1- dimethylethyl) phenol derivatives" (*Farmaco* **48** (10) 1463-73, 1993);

Kurokawa M "Synthesis and antiinflammatory activity of cis- and trans- 6,6a, 7,8,9,10,10a,11- octahydro-11-oxodibenzo[b,e]thiepinacetic and -oxepinacetic acids"

(*Journal of Medicinal Chemistry* **33** (2) 504-9, 1990);

Uren M F, "The effect of anti-inflammatory agents on the clinical expression of bovine ephemeral fever" (*Veterinary Microbiology* **19** (2) 99-111, 1989;

Crossley M J, "Studies on the effects of pharmacological agents on antigen-induced arthritis in BALB/c mice" (*Drugs Under Experimental and Clinical Research* **13** (5) 273-7, 1987).

Thus, structure/activity relationships involving VLA-4 are unpredictable. Perhaps it is true that many of the compounds falling within the scope of claim 35 will exhibit an IC_{50} of 15 *micro*molar in an assay of VLA-4. However, the significance of this number (15 μM) with respect to treatment of treatment of Alzheimer's disease, AIDS dementia, diabetes, atherosclerosis, multiple sclerosis, inflammatory bowel disease, stroke, nephritis, asthma, retinitis, atopic dermatitis, psoriasis, and myocardial ischemia is unknown. No correlation has been established between this "15 μM" parameter, and successful treatment of any of the foregoing diseases. Moreover, other issues such as bioavailability and pharmacokinetics are not reflected in this "15 μM" number.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988), the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As is evident, extrapolation from

an observation of VLA-4 binding in vitro to treatment of Alzheimer's disease, AIDS dementia, diabetes, atherosclerosis, multiple sclerosis, inflammatory bowel disease, stroke, nephritis, asthma, retinitis, atopic dermatitis, psoriasis, and myocardial ischemia will produce "unpredictable" results.

In response to the foregoing, applicants have asserted that if a drug is "active" *in vivo* at a concentration of less than 100 μM, it will be a useful drug. However, applicants do not explain what they mean by "active". If by "active", applicants intend that the compound merely binds *alpha* 9 *in vitro*, then the assertion that one can extrapolate from this in vitro result to an effective *in vivo* therapy is unsubstantiated and unpersuasive. In reality, the skilled artisan cannot predict therapeutic efficacy in the treatment of human disease on the basis of an *in vitro* finding of integrin binding. Alternatively, the term "active" could mean that, after an exhaustive (and "undue") study of thousands of compounds, one compound is found that is therapeutically effective at a concentration of 100 μM in the bloodstream or other unspecified tissue. Certainly, there are many drugs that are effective to treat human disease at a concentration less than 100 μM in the bloodstream. But the fact that this may be true has no bearing on the claimed invention. The fact that there may exist other drugs (not *alpha* 9 antagonists) which are effective does not, in any way, constitute evidence that *alpha* 9 antagonists can be used to treat a human disease. If applicants have evidence that *alpha* 9 antagonists can be used to treat a human disease at a

concentration below 100 μM in the bloodstream (or other tissue), it is suggested that applicants make the same of record. Otherwise, the assertion that *alpha* 9 antagonists can be used to treat a human disease at a concentration below 100 μM in the bloodstream (or other tissue) constitutes little more than idle speculation.

Applicants argue that the specification provides "considerable guidance" to enable a skilled artisan to use an alpha 9 antagonist to treat human disease. However, no page or line numbers have been provided which shows the skilled artisan how to use alpha 9 antagonists in this way. Certainly, the specification contains speculation as to what a person might, at some point in the future, try to do. But as for teaching the skilled artisan to use alpha 9 antagonists to treat human disease, there is absolutely no information given on this subject. Applicants have further implied that it would be a simple matter of routine experimentation to test all possible alpha 9 antagonists for efficacy in animal models of Alzheimer's disease, AIDS dementia, diabetes, atherosclerosis, multiple sclerosis, inflammatory bowel disease, stroke, nephritis, asthma, retinitis, atopic dermatitis, psoriasis, and myocardial ischemia. If this represents applicants view on the matter, it is suggested that applicants undertake an amount of experimentation that they regard as "routine", and that the results be presented.

Applicants have also argued that it is not necessary that all compounds be equally effective. However, this argument does not amount to a response to any of the examiner's arguments. The question at this particular point in the prosecution is, does there exist even

one *alpha* 9 antagonist (that is specifically identified in the specification) which will effectively treat one of the human diseases that is recited in the specification? Based on the evidence thus far, the answer is in the negative.

Clearly then, "undue experimentation" would be required to practice the claimed invention. In addition to the foregoing arguments, consider the following:

- Pierce, J. W., ("Salicylates inhibit I kappa B-alpha phosphorylation, endothelial-leukocyte adhesion molecule expression, and neutrophil transmigration", Journal of Immunology, 156 (10) 3961-9, 1996) discloses that aspirin inhibits ICAM-1 and VCAM-1 expression. In a similar vein, Gonzalez-Alvaro I ("Interference of nonsteroidal antiinflammatory drugs with very late activation antigen 4/vascular cells adhesion molecule 1-mediated lymphocyte-endothelial cell adhesion", Arthritis and Rheumatism 41 (9) 1677-88, 1998) discloses that indomethacin inhibits VLA-4/VCAM-1 interactions. If applicants' assertions were correct, the skilled artisan would predict that success in the treatment of inflammatory conditions would be achieved by any compound which antagonizes VLA-4/VCAM-1 interactions. Yet this is not what one finds. For example, Goldenberg M M ("A pharmacologic analysis of the action of platelet-activating factor in the induction of hindpaw edema in the rat", Prostaglandins 28 (2) 271-8, 1984) discloses that neither indomethacin nor aspirin was effective to inhibit an inflammatory response to paw edema in rats. Similarly, Zuany-Amorim C. (European Journal of Pharmacology 257 (3) 211-6, 1994), discloses that aspirin failed to inhibit inflammatory responses to antigen (e.g., page 214, col 1). These findings of Goldenberg and of Zuany-Amorim support the examiner's contention that one cannot predict success in the treatment of inflammatory diseases merely because one can antagonize VLA-4/VCAM-1 interactions in vitro. As two more examples, Rordorf C "Arthritis in MRL/LPR mice and in collagen II sensitized DBA-1 mice and their use in pharmacology", International Journal of Tissue Reactions 9 (4) 341-7, 1987 discloses that indomethacin was not effective to treat arthritis in an animal model, and Goldlust M B (Agents and Actions 11 (6-7) 729-35, 1981) discloses that aspirin was not effective to treat synovitis in rabbits.

- Theien, B. E. (*Journal of Clinical Investigation* **107** (8) 995-1006, 2001) compared

the ability of anti-VLA-4 to regulate proteolipid protein (PLP) 139-151-induced R-EAE when administered either before or after disease onset. Preclinical administration of anti-VLA-4 either to naive recipients of primed encephalitogenic T cells or to mice 1 week after peptide priming, i.e., before clinical disease onset, inhibited the onset and severity of clinical disease. In contrast, Ab treatment either at the peak of acute disease or during remission exacerbated disease relapses and increased the accumulation of CD4(+) T cells in the CNS. Most significantly, anti-VLA-4 treatment either before or during ongoing R-EAE enhanced Th1 responses to both the priming peptide and endogenous myelin epitopes released secondary to acute tissue damage. Collectively, these results suggest that treatment with anti-VLA-4 Ab may be problematic in treating established autoimmune diseases such as MS. Accordingly, one cannot predict success in the treatment of MS based on the propensity of a compound to antagonize VLA-4.

- Saez-Torres I ("Peptide T does not ameliorate experimental autoimmune encephalomyelitis (EAE) in Lewis rats", *Clinical and Experimental Immunology* **121** (1) 151-6, 2000) discloses that it is known in the art that peptide T inhibits T cell activation and cytokine production and function. Saez-Torres studied the ability of peptide T to ameliorate EAE in Lewis rats. Peptide T was administered subcutaneously at different doses and phases of the disease according to several treatment protocols. The authors concluded that peptide T neither prevents nor ameliorates EAE in Lewis rats. This supports the conclusion that one cannot "predict" success in the treatment of inflammatory conditions, even if one is able to inhibit T cell activation and cytokine production. This finding of Saez-Torres is relevant in part because VLA-4 is prominently expressed on circulating T-cells.

The foregoing teachings further support the conclusion that one cannot predict efficacy in the treatment of human disease merely by modulating *alpha* 4/ligand interactions in vitro (or VLA-9/ligand interactions). Clearly, "undue experimentation" would be required to practice the claimed invention.

*

Claims 31-47 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for

failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 45 recites the phrase "said compound". However, it is unclear what this is referring to. It could be referring to the antagonist compound of claim 41, or it could be referring to one of the compounds referred to in claim 44. The claim interpretation is entirely different depending on which of these two interpretations applies. This is because claim 44 includes, but is not limited to the nine listed compounds. In any case, claim 45 should be made clear as to what exactly is meant by "said compound".

- Claims 37-39 are indefinite as to the intended inflammatory conditions.

- Claim 37 recites the phrase "pharmaceutically effective", thus rendering the claims indefinite as to the objectives of the pharmaceutically efficacy. The claim is also indefinite as to the manifestations of a successful treatment. For example, if the disease is asthma, would it be sufficient if there were a detectable change in eosinophil levels following treatment, or would it be necessary that there be a measurable improvement in lung capacity? When one knows which disease is being treated, it is difficult enough to ascertain what applicants may intend for the endpoint. But when the skilled artisan cannot determine if a given disease is even encompassed, the task of determining what might be encompassed becomes insurmountable.

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claim 33 is rejected under 35 U.S.C. 102 (e) as being anticipated by Lin (USP 6,248,713).

Lin discloses various VLA-4 inhibitors that can be used to treat inflammatory diseases, including those encompassed by claim 33. Lin does not disclose that the compounds will antagonize VLA-9.

Claim 33 could be interpreted in either of two ways: (a) the compound must be an antagonist of both alpha 4 and alpha 9, or (b) if a compound is an antagonist of alpha 4, then it is inevitably an antagonist of alpha 9. According to this second interpretation, the property of being an alpha 9 antagonist is inherent in any compound that is an alpha 4 antagonist. According to this interpretation, the claim is anticipated by any reference that discloses an alpha 4 antagonist.

Thus, the claim is anticipated.

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 31-47 are rejected under 35 U.S.C. §103 as being unpatentable over Smith (*J Biol Chem* **271**, 28485, 1996).

Smith discloses that osteopontin binds to an *alpha*-9 integrin, and that an N-terminal fragment of osteopontin also binds to *alpha*-9 integrin. Thus, both osteopontin and the fragment thereof are *alpha* 9 antagonists.

With respect to claim 37, one of ordinary skill would have expected that all *alpha*-9 integrin antagonists will be effective in treating any disease with which an alpha 9 integrin is at least remotely connected. And certainly (claim 41), if a compound binds to *alpha* 9, that compound will inhibit binding of *alpha* 9 to other *alpha*-9 ligands.

Consider next claim 44. This claim makes reference to <u>any</u> *alpha* 9 ligand; as such, the ligand can be osteopontin. Thus, for example, osteopontin will inhibit the binding between the disclosed osteopontin fragment and *alpha* 9, and vice versa; i.e., the

osteopontin fragment will inhibit binding between osteopontin and *alpha* 9. One would expect that the potency of the osteopontin (and the fragment) to achieve this would be greater than that exhibited by any of the compounds recited in claim 44. Claim 44 permits at least three orders of magnitude less binding than would be expected for the recited compound with the worst binding, so the case for obviousness is on firm ground. Furthermore, while the compounds recited in claim 44 may be antagonists of VLA-4, it remains an open question as to whether they exhibit any binding at all to *alpha* 9. Claim 45 is rejected, since "said compound" could refer to the compound referred to in claim 44, rather than that which is referred to in claim 41.

*

Claims 31-47 are rejected under 35 U.S.C. §103 as being unpatentable over Palmer (*J Cell Biol* **123**, 1289, 1993).

Palmer discloses (e.g., p. 1290, col 2; p. 1293, col 2) antibodies to *alpha*-9. Palmer does not disclose that if *alpha*-9 is bound to anti-*alpha* 9 antibodies, binding of other *alpha* 9 ligands will be perceptibly diminished. However, a biochemist or immunologist of ordinary skill would have expected some competition between the two ligands to occur, especially given the notoriously tight binding between antibodies and the proteins to which they have been directed. The skilled artisan would have further reasoned that given the involvement of *alpha* 9 in various diseases, any antagonist of *alpha* 9 will be effective to mitigate symptoms of the disease. Such an antagonist would include antibodies to alpha

9. As for claim 44, the listed compounds have only been shown to antagonize *alpha*-4. While it is possible that the compounds also antagonize *alpha* 9, the skilled immunologist would have expected that antibodies to *alpha*-9 will be even better antagonists of *alpha*-9 than antagonists of *alpha*-4 will be antagonists of *alpha*-9. Claim 45 is also rejected, since "said compound" can refer to the compounds of claim 44, which only serve as benchmarks, i.e., claim 45 does not actually require that compounds of the following formula are being used to inhibit the binding of ligands:

$$R^1\text{-}SO_2\text{-}NR^2\text{-}CHR^3\text{-}Q\text{-}CHR^5\text{-}COOH$$

Thus, the claims are rendered obvious.

*

Claims 31-47 are rejected under 35 U.S.C. §103 as being unpatentable over Lin (USP 6,248,713) in view of Palmer (*J Cell Biol* **123**, 1289, 1993).

Lin discloses compounds that are effective to antagonize VLA-4. Palmer discloses that *alpha* 4 and *alpha* 9 exhibit sequence and structural homology to one another. Thus, it would have been obvious to one of ordinary skill that if a compound is an antagonist of VLA-4, it will also antagonize *alpha*-9, although perhaps to a lesser degree.

Thus, the claims are rendered obvious.

*

Claims 31-47 are rejected under 35 U.S.C. §103 as being unpatentable over Yokosaki, Yasuyuki (*J. Biol Chem* **269**(43), 26691-96, 1994).

Yokosaki discloses that tenascin binds to *alpha* 9. One of ordinary skill would have reasoned that if a compound binds to *alpha* 9, it must be an *alpha* 9 antagonist, and further, that it can be used to treat any *alpha* 9-mediated disease. Thus, it would have been obvious to one of ordinary skill that tenascin is an *alpha* 9 antagonist, and that tenascin can be used to treat any *alpha* 9-mediated disease.

*

Claims 31-47 are rejected under 35 U.S.C. §103 as being unpatentable over Yokosaki, Yasuyuki (*J. Biol Chem* **269**(43), 26691-96, 1994).

One of the teachings of Yokosaki is indicated above. Another teaching is that (e.g., page 26695, col 1) the binding of alpha-9 transfected cells to tenascin is inhibited by antibodies to beta-1. It would appear then that an antibody to *beta*-1 would actually qualify as an *alpha*-9 antagonist within the meaning of the instant claims. The reason is that the claims do not mandate that *alpha* 9 be present as a monomer, but instead encompass the possibility that the *alpha* 9 is present as a dimer with *beta* 1 (or with any other protein, for that matter). Accordingly, Yokosaki discloses that an anti-*beta* 1 antibody is a VLA-9 antagonist. One of ordinary skill would expect that any VLA-9 antagonist will be effective to treat any VLA 9 – mediated disease.

Thus, the claims are rendered obvious.

*

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800